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REVIEW

Progress of clinical research on targeted therapy combined with thoracic radiotherapy for non-small-cell lung cancer

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Abstract: The combination of radiotherapy and targeted therapy is an important approach in the application of targeted therapy in clinical practice, and represents an important opportunity for the development of radiotherapy itself. Numerous agents, including epidermal growth factor receptor, monoclonal antibodies, tyrosine kinase inhibitors, and antiangiogenic therapies, have been used for targeted therapy. A number of studies of radiotherapy combined with targeted therapy in non-small-cell lung carcinoma have been completed or are ongoing. This paper briefly summarizes the drugs involved and the important related clinical research, and indicates that considerable progress has been made with the joint efforts of the two disciplines. Many issues, including drug selection, identification of populations most likely to benefit, timing of administration of medication, and side effects of treatment require further investigation. However, further fundamental research and accumulation of clinical data will provide a more comprehensive understanding of these therapies. Targeted therapy in combination with radiotherapy has a bright future.

Keywords: non-small-cell lung carcinoma, radiotherapy, epidermal growth factor receptor, monoclonal antibody, tyrosine kinase inhibitors, antiangiogenic therapies

Introduction

Targeted therapy is a type of medication that blocks the growth of cancer cells by interfering with the specific molecules needed for carcinogenesis and tumor growth, rather than by simply interfering with all rapidly dividing cells. The combination of radiotherapy and targeted therapy is an important approach for application of targeted therapy in clinical practice and represents an opportunity for the further development of radiotherapy itself.

Radiotherapy combined with targeted therapy has considerably furthered the study of non-small-cell lung carcinoma (NSCLC) under the joint efforts of the two disciplines, yielding both exciting results and worrisome reports. However, studies involving targeted therapy have gradually produced cumulative data on the subject. Differences in the experimental results prompted this summary for a more comprehensive and rational understanding of radiotherapy combined with targeted therapy. This retrospective review of the literature indicates that numerous drugs have been used for targeted therapy and that the studies of radiotherapy combined with targeted therapy are diverse and complicated by their variable quality.

Radiotherapy combined with EGFR monoclonal antibodies

Preclinical studies suggested that the epidermal growth factor receptor (EGFR) monoclonal antibody was a radiation-sensitizing agent because it increased the rate

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of apoptosis, regulated the cell cycle, reduced radiation resistance, and increased radiation injuries.[1] Early clinical studies of the EGFR monoclonal antibody in combination with radiotherapy primarily included head and neck squamous cell carcinoma, and the study of its combination with radiation therapy for NSCLC was performed relatively late. The EGFR monoclonal antibodies include cetuximab, nimotuzumab, and panitumumab. Clinical research has primarily focused on cetuximab, with fewer studies of the other two drugs. Hughes et al[2] determined the safety of thoracic radiotherapy combined with cetuximab in the SCRATCH study, and Hallqvist et al[3] and Kotsakis et al[4] conducted two higher quality Phase II clinical studies demonstrating that the toxicity of thoracic radiotherapy combined with cetuximab for NSCLC was similar to that of radiotherapy alone and that cetuximab was slightly more toxic in terms of cutaneous reactions. The remaining studies primarily investigated cetuximab with concurrent chemoradiotherapy;[5–7] their results indicate that treatment-related toxicity was similar to that occurring with simple concurrent radiotherapy and that the rate of cetuximab-induced grade 3 skin toxicity was approximately 6%–20%. The results of the cetuximab with radiotherapy or chemoradiotherapy studies mentioned above indicate an overall survival rate of approximately 17–25 months in patients with stage III NSCLC, an incidence of grade 3 or higher radiation pneumonitis of approximately 4%–12%, and an incidence of grade 3 or higher esophageal inflammation of approximately 4%–20%. These early studies demonstrated that the toxicity of cetuximab with concurrent radiotherapy or chemoradiotherapy was acceptable but that its impact on the survival of patients with locally advanced NSCLC was minor.

The preliminary results of a recent prospective randomized Phase III clinical study (RTOG-0617)[8] provided updated evidence of the impact of cetuximab with concurrent chemoradiotherapy on survival in patients with stage III NSCLC. This study investigated 465 patients receiving cetuximab over a median follow-up period of 18.7 months. Cetuximab was given on a base of carboplatin and docetaxel chemotherapy with concurrent radiotherapy. The median overall survival in patients receiving chemoradiotherapy with cetuximab and chemoradiotherapy alone was 23.1 months and 23.5 months, respectively; overall survival at 18 months was 60.8% and 60.2% (hazard ratio 0.99; P=0.484) and median progression-free survival was 10.4 months and 10.7 months. The overall incidence of combined adverse events for patients receiving chemoradiotherapy with cetuximab and chemoradiotherapy alone was 85.2% and 69.5%, respectively (P<0.0001), and the overall incidence of nonhematologic adverse events was 70.5% and 50.7% (P<0.0001). These findings indicate that addition of cetuximab to a base of chemoradiotherapy did not benefit patients with unresectable stage III NSCLC. However, more side effects occurred. Subgroup analysis showed that patients with high EGFR expression had better responses to cetuximab, but the impact of this drug on survival requires further investigation.

Nimotuzumab showed benefits when combined with concurrent chemotherapy in the treatment of head and neck cancers. Nimotuzumab with chemoradiotherapy for NSCLC is currently being investigated. Zhou et al[9] have reported their preliminary results for nimotuzumab with radical radiotherapy for stage III squamous cell lung carcinoma and found no side effects, including rashes and allergies, attributable to nimotuzumab (Table 1). However, to acquire more detailed results and determine the impact on survival, further investigation is required. Research on panitumumab with concurrent chemoradiotherapy in stage III NSCLC is also under way (ClinicalTrials.gov identifier NCT00979212), but no results have been published as yet.

TKIs and radiotherapy

The tyrosine kinase inhibitors (TKIs) primarily include gefitinib and erlotinib. Fundamental research shows that the radiosensitivity mechanism of TKIs is similar to that of EGFR monoclonal antibodies, but the results of clinical trials have not been identical. In an early Phase II study (CALGB 30106) of gefitinib with thoracic chemoradiotherapy for stage III NSCLC,[10] concurrent or subsequent thoracic chemoradiotherapy was designed for gefitinib followed by gefitinib for maintenance. However, this study was closed prematurely because of the results of the S0023 study[11] in which gefitinib showed no benefit in maintenance therapy compared with placebo. The survival rate for the 63 patients in this study was not improved significantly when compared with standard concurrent chemoradiotherapy. Overall survival was 13 months in the high-risk group (95% confidence interval [CI] 8.5–17.2) and 19 months in the low-risk group (95% CI 9.9–28.4). Rothschild et al[12] and Ball et al[13] reported two Phase I clinical studies of gefitinib with concurrent thoracic radiotherapy or thoracic chemoradiotherapy, in which clinical toxicity could be tolerated but survival was not significantly improved. Center et al[14] and Stinchcombe et al[15] increased the dose of thoracic radiotherapy to 70 Gy, but their survival results were also disappointing.

Gefitinib with thoracic radiotherapy provides small benefits in Asian populations. Ohe et al[16] administered

Table 1 Published trials of key agents in combination with radiotherapy

Therapy	Reference	Phase clinical setting	Patients (n)	Induction	Concurrent	Consolidation/ maintenance	Radiotherapy	Median OS (months)	Toxicity
Cetuximab	Hughes et al[2]	I	12	Platinum-based chemotherapy	Cetuximab	–	64 Gy/32 fractions	N/A	Grade 3 fatigue (8%) and pneumonia (8%); grade 5 bronchopneumonia (one patient)
	Hallqvist et al[3]	II	75	Cisplatin/docetaxel	Cetuximab	–	68 Gy/34 fractions	17	Grade 3 esophagitis (1.4%); skin reactions (11.3%); grade ≥3 pneumonia (4.2%)
	Kotsakis et al[4]	II	38	–	Cetuximab	Carboplatin + paclitaxel + cetuximab	73.5 Gy/ 35 fractions	17.1	Grade 3 fatigue (5%); grade 5 pneumonia (one patient); no patient with grade ≥3 esophagitis
	RTOG-0617 Masters et al[8]	III	465	–	Carboplatin + paclitaxel + cetuximab	–	60 Gy/30 fractions	23.1	Grade ≥3 nonhematologic toxicity 70.5%; grade 4/5 nonhematologic toxicity 35.8%
Nimotuzumab	Zhou et al[9]	II	11	–	Carboplatin + docetaxel + nimotuzumab	Carboplatin + docetaxel	50–66 Gy/ 25–30 fractions	Not reached	Grade 3 pneumonia (18.2%); esophagitis (18.2%); thrombocytopenia (18.2%); grade 4 neutropenia (36.4%)
Gefitinib	CALEB 30106 Ready et al[10]	II	Poor risk status 1: 21 Good risk status 2: 29	Carboplatin/ paclitaxel	Gefitinib	Gefitinib	66 Gy/33 fractions	Status 1: 19 Status 2: 13	Status 1: grade ≥3 pneumonia (15%); esophagitis (19%); fatigue (24%); electrolyte disturbances (10%); diarrhea (10%) Status 2: grade ≥3 pneumonia (16%); esophagitis (31%); fatigue (33%); electrolyte disturbances (16%); diarrhea (18%)
	Rothschild et al[12]	I	Step 1: 5 Step 2: 9	–	Step 1: Gefitinib Step 2: Gefitinib + cisplatin	Both steps: Gefitinib	45 Gy/25 fractions and then 18 Gy/9 fractions boost primary and involved nodes	382 days combined	Step 2: One patient with grade 3 pneumonia and one patient with grade 2 hepatic enzyme increase
	Ball et al[13]	I	28	–	Carboplatin + gefitinib ± paclitaxel	± Surgery	60 Gy/30 fractions	N/A	No DLTs observed
	Center et al[14]	I	16	–	Docetaxel + gefitinib	Docetaxel	70 Gy/35 fractions	21	Grade 3/4: hematologic (27%); esophagitis (27%) Grade 3/5: lung toxicity (20%), two patients with grade 5 lung toxicity
	Stinchcombe et al[15]	I	23	Carboplatin/ paclitaxel/irinotecan + pegfilgrastim	Carboplatin + paclitaxel + gefitinib	–	74 Gy/37 fractions	16	Grade 3: esophagitis (19.5%); one patient with late spinal cord syndrome

(*Continued*)

Table 1 (*Continued*)

Therapy	Reference	Phase clinical setting	Patients (n)	Induction	Concurrent	Consolidation/ maintenance	Radiotherapy	Median OS (months)	Toxicity
	Ohe et al[16]	II	38	Vinorelbine + cisplatin	Gefitinib	Gefitinib	60 Gy/30 fractions	28.1	Grade ≥2: pneumonia (5%); grade 3/4 transaminase elevation (37%)
Gefitinib/ erlotinib	Wang et al[17]	II	Gefitinib: 19 Erlotinib: 7	–	Gefitinib/ erlotinib	Gefitinib/ Erlotinib	Median: 70 Gy/30 fractions; individualized SBRT	21.8	Grade 3: esophagitis (4%); fatigue (4%); pneumonia (4%)
Erlotinib	Komaki et al[18]	II	48	–	Carboplatin + paclitaxel + erlotinib	Paclitaxel	63 Gy/35 fractions	25.8	Grade 3: acne (two patients); esophagitis (one patient); pneumonia (two patients)
	Ramella et al[19]	II	60	–	Pemetrexed + erlotinib or gemcitabine + erlotinib	–	50.4–59.4 Gy/ individualized fractions	14.4 (non-squamous carcinoma); 4.9 (squamous carcinoma)	Grade 3: rash (7%) Grade ≥3: esophagitis (2%); pneumonia (5%); hepatic enzyme increase (16.6%)
	Wan et al[20]	I/II	8	Erlotinib	Erlotinib 100 mg or 150 mg daily	Erlotinib	45 Gy/15 fractions or 60 Gy/ 30 fractions	N/A	In 60 Gy/30 fractions and 150 mg/day erlotinib arm, one patient with grade 5 pneumonia and one patient with grade 3 pneumonia
Bevacizumab	Lind et al[24]	I	6	Cisplatin-based	7.5 mg/kg or 15 mg/kg	–	66 Gy/33 fractions	N/A	Two patients with grade 3 pneumonia; two patients with grade 2 pneumonia
	Socinski et al[27]	II	45	Bevacizumab + paclitaxel + carboplatin	Bevacizumab + paclitaxel + carboplatin ± erlotinib	Erlotinib + bevacizumab	74 Gy/37 fractions	18.4	Grade ≥2: esophagitis (53.8%); Grade 3/4: esophagitis (29%); one patient with grade 3 tracheoesophageal fistula
	Spigel et al[25]	II	29	Irinotecan + carboplatin	Irinotecan + carboplatin + bevacizumab	Bevacizumab	61.2 Gy	N/A	Grade 3/4 toxicity included: diarrhea (21%), esophagitis (14%), fatigue (17%), pain (14%), neutropenia (18%), leukopenia (10%), and thrombocytopenia (28%). Two patients with tracheoesophageal fistula (one resulting in death); one patient died from an aerodigestive hemorrhage
Endostatin	Zhou et al[31]	I/II	47	–	Docetaxel + cisplatin + endostatin	–	60–66 Gy/ 30–33 fractions		Grade 3/4: esophagitis (8.5%); pneumonia (11%); one patient with grade 5 pneumonia

Abbreviations: OS, overall survival; DLT, dose-limiting toxicity; SBRT, stereotactic body radiotherapy; N/A, not available.

gefitinib with thoracic radiotherapy in Japanese patients with unresectable NSCLC who had undergone induction chemotherapy, and the results of the Phase II clinical study showed an encouraging median survival time of 28 months. However, only about 61% of patients completed the treatment, and the remaining patients discontinued treatment because of grade 2 or higher radiation pneumonitis. Wang et al[17] investigated EGFR TKI therapy with thoracic radiotherapy for NSCLC and reported that the occurrence of radiation pneumonitis was not severe. Therefore, the toxicity of gefitinib with thoracic radiotherapy and survival requires further study. More stringent control of the lung dose and selection of populations likely to benefit from such treatment should direct future research.

Erlotinib with thoracic radiotherapy has achieved relatively good results. Komaki et al[18] investigated erlotinib with thoracic chemoradiotherapy for unresectable stage III NSCLC. A clinical program of erlotinib 150 mg/day with concurrent thoracic radiotherapy (63 Gy/35 fractions) and a chemotherapy program of paclitaxel and carboplatin followed by two cycles of paclitaxel and carboplatin chemotherapy in sufficient doses were designed. Grade 3 esophagitis occurred in only one of the 48 enrolled patients, and radiation pneumonitis occurred in three cases. No grade 4–5 treatment-related side effects were observed. Median progression-free survival and overall survival were 13.6 months and 25.8 months, respectively. Only 12% of the enrolled patients showed the EGFR-related site-sensitive mutation.

Ramella et al[19] reported another Phase II clinical study of erlotinib with gemcitabine or pemetrexed and concurrent thoracic radiotherapy (50.4–59.4 Gy) for patients with recurrence of disease after chemotherapy and showed better efficacy and acceptable toxicity. Subgroup analysis showed that overall survival (14.4 months versus 4.9 months, P=0.01) and progression-free survival (7.5 months versus 4.6 months, P=0.06) of patients with non-squamous cell carcinoma (40 cases) were better than in patients with squamous cell carcinoma (20 cases).

However, in another study, Wan et al[20] investigated erlotinib with thoracic radiotherapy for stage III NSCLC in patients with poor general performance status (ie, 2). Fatal grade 5 radiation pneumonitis occurred in one of the five patients receiving erlotinib 150 mg/day, and grade 3 radiation pneumonitis occurred in one case. These side effects prompted premature closure of this study. A retrospective study by Chang et al[21] documented radiation pneumonitis in 21 of 25 enrolled patients treated with erlotinib or gefitinib and thoracic radiotherapy, and two of these cases were grade 5 (Table 1).

Some clinical trials of TKI with thoracic radiotherapy or thoracic chemoradiotherapy are currently in progress (NCT00620269, NCT00553462, NCT01091376 for erlotinib; NCT01391260 for gefitinib). These studies have greater depth and focus more on populations with EGFR mutations or those in poor general condition. More studies of TKIs with thoracic radiotherapy or thoracic chemoradiotherapy have been performed, with some suggesting that TKIs enhance the efficacy of radiotherapy; however, randomized controlled large-scale studies are lacking. The issue of radiation pneumonitis and esophageal toxicity when TKIs are combined with thoracic radiotherapy requires further investigation.

Radiotherapy with antiangiogenic therapies

The antiangiogenesis drugs currently available are bevacizumab and endostatin. Few studies have been reported on vascular blockers, antiangiogenesis drugs, drugs inhibiting degradation of the basement membrane, and agents inhibiting cell integrin, and are not described in this report. The antiangiogenic sites for bevacizumab and endostatin are different, but their radiosensitivity mechanisms are similar. Numerous preclinical studies have shown that these agents exert their radiation-sensitizing properties via the promotion of oxygenation by rationalizing the blood vessels of the tumor, inhibiting the radiation-induced increase in vascular endothelial growth factor expression, and reducing their resistance to complement each other, leading to enhancement of the antitumor effects.[22,23]

Clinical research is somewhat lacking in comparison with fundamental research. Several early Phase I–II studies of bevacizumab with thoracic radiotherapy were closed prematurely because of side effects, such as radiation esophagitis, esophageal fistula, and radiation pneumonitis, and clinical data regarding patient survival have not been reported.[24–26] Socinski et al[27] reported a clinical study of thoracic radiotherapy with bevacizumab and erlotinib for stage III NSCLC. Patients underwent induction chemotherapy of paclitaxel and carboplatin with bevacizumab, and then received concurrent chemoradiotherapy and bevacizumab. The radiation dose was 74 Gy, the concurrent paclitaxel dose was 45 mg/m^2, carboplatin was given weekly in accordance with an area under the curve of 2, and bevacizumab 10 mg/kg was administered twice weekly. Erlotinib was either not administered during radiotherapy,

or administered at doses of 100 mg/day, or 150 mg/day. Maintenance therapy with erlotinib and bevacizumab was continued after chemoradiotherapy. The objective response rate was 60% (95% CI 44–75) in the 45 enrolled patients, median progression-free survival was 10.2 months (95% CI 8.4–18.3), and median overall survival was 18.4 months (95% CI 13.4–31.7). Concurrent chemoradiotherapy did not improve the outcome when compared with standard treatment for localized advanced NSCLC. The incidence of grade 3 esophagitis was 19.2% in this study and the incidence of grade 2 esophagitis was 53.8%.

A Phase I clinical study (NCT00531076)[24] of bevacizumab with radiotherapy in patients with unresectable locally advanced NSCLC was closed prematurely because of a high incidence of radiation pneumonitis. A total of six patients were enrolled in this study; two developed grade 2 radiation pneumonitis and two developed grade 3 radiation pneumonitis. A Phase II clinical study of bevacizumab with concurrent chemoradiotherapy in small cell lung cancer[25] reported severe tracheal esophageal fistula in two of 29 enrolled patients, and another three patients died of massive hemorrhage of unknown cause (suspected tracheoesophageal fistula). Grade 3 esophagitis occurred in all patients receiving maintenance therapy with bevacizumab after concurrent chemoradiotherapy. Other studies have reported similar results.[28,29]

Several studies have reported that bevacizumab with thoracic chemoradiotherapy does not improve treatment efficacy but increases the risk of side effects. Ma et al[30] investigated concurrent administration of thoracic radiotherapy and endostatin for unresectable stage III NSCLC. However, this study was closed prematurely because grade 3 or higher radiation pneumonitis occurred in four of the 12 enrolled patients. The Cancer Hospital of Sun Yat-sen University has reported the results of a multicenter Phase I–II clinical trial of endostatin with concurrent chemoradiotherapy for unresectable stage III NSCLC.[31] A total of 47 patients were enrolled in the study from 2009 to 2011. Patients received three-dimensional conformal radiotherapy of 60–66 Gy for 6–7 weeks concurrent with two cycles of chemotherapy comprising docetaxel 65 mg/m^2 and cisplatin 65 mg/m^2. Daily intravenous endostatin 7.5 mg/m^2 was administered one week before radiotherapy and in weeks 2, 4, and 6. Forty-four patients completed the efficacy and safety assessments, and 42 completed the assessment of short-term efficacy; there were five cases of complete remission, 29 cases of partial remission, three cases of stable disease, and five cases of progression, giving an efficacy rate of 77%. One-year survival and progression-free survival was 81% and 51%, respectively. Of the 12 deaths, eight were from cancer, two were of unknown cause, one was the result of infection, and one because of radiation pneumonitis. Grade 3 acute radiation esophagitis and pneumonitis occurred in four patients, and grade 5 radiation pneumonitis occurred in one case. In summary, no large-scale clinical studies of radiotherapy with antiangiogenic drugs for NSCLC have been reported (Table 1). More evidence is required from clinical trials to determine the efficacy and safety of antiangiogenic drugs with thoracic radiotherapy for NSCLC.

Current problems with concurrent radiotherapy and targeted therapy

Selection of advantageous drugs for targeted therapy with radiotherapy

Few comparative studies are available on the efficacy of targeted drugs in combination with radiotherapy. Therefore, drug selection presently lacks supportive clinical evidence. The results for simultaneous combinations of drugs with different mechanisms of action and radiotherapy to maximize the enhancing effect of radiotherapy are not conclusive.[32] However, numerous factors drive angiogenesis and degradation and occlusion of blood vessels. Therefore, a single antiangiogenic drug, even drugs with the same mechanism such as antiangiogenic therapies, cannot completely solve the vascular problems. Whether combinations of different antivascular agents would improve tumor suppression is not known.[33] For example, bevacizumab with endostatin inhibits vascular endothelial growth factor and exerts an antitumor effect via changes in proliferation of vascular endothelial cells. Furthermore, radiation itself is an important antiangiogenic therapy, and combination of different antiangiogenic therapies improves the therapeutic effect. However, two problems have arisen. First, the effect of activation of additional factors using combinations of several treatment modalities on the organization and control of tumor angiogenesis is not known. Second, the adverse consequences of a combination of several treatment modalities require further investigation. EGFR monoclonal antibodies and TKIs inhibit EGFR but have yielded different results in clinical trials; the reasons underlying this differential effect are not known. These inconsistent results challenge drug selection for radiotherapy in combination with targeted therapy.

Selection of populations likely to benefit from targeted therapy with radiotherapy

The selection of populations likely to benefit from targeted therapy with radiotherapy is problematic. EGFR mutations

at related sites are an important indicator of therapeutic sensitivity for some targeted therapies, such as TKIs. However, the relevance of EGFR mutation to efficacy in radiotherapy with a TKI is not known. This problem has arisen for several reasons. First, few studies are available on the issue of efficacy. Experimental studies in vitro showed that tumor cells with mutations are more sensitive to radiation,[34,35] but this comparison was between different cell lines. The EGFR mutations were different, but the effects of other genes present in the cells being compared could not be excluded. The relationship between radiation and mutations is not known. This study could not establish efficacy in tumor cell samples derived from the same cell lines with only different EGFR site mutations. Second, whether there is a significant increase in the tumoricidal activity of a TKI when it was combined with radiotherapy is not known because either treatment alone kills tumor cells. The determining role of the EGFR mutation may be weakened under the dual functions of radiotherapy and TKI. Third, tumor heterogeneity and limitations in the detection of EGFR mutation itself complicate the analysis. The uncertainty of the EGFR mutation itself, the lack of dynamic monitoring, and the lack of a unified detection platform may also contribute to the uncertainty of EGFR mutation detection.[36] Therefore, many factors affect the relationship of the efficacy and predictors of radiotherapy with targeted therapy. A large-scale, randomized controlled study is a better way of answering these questions.

Optimization of targeted therapy with radiotherapy

This is a relatively complex issue, with numerous aspects, such as timing, duration, and administration dose, needing to be taken into account. Different administration timing for antiangiogenic therapies is based on different theories. Induction therapy primarily normalizes the blood vessels. Concurrent administration primarily inhibits the radiation-induced increase in vascular endothelial growth factor expression and consolidates that administration, which may relate cell death in the proliferative phase. Specific timing of administration may play a more important role, but the relevant research is lacking. Administration prior to radiotherapy based on the vascular normalization theory is currently accepted but problematic. The time window of vascular normalization is approximately 6 days,[37,38] and radiotherapy is hyperfractionated for administration 5 times per week. Radiotherapy also plays an important part in the occlusion of local vessels. Optimization of antiangiogenic therapy concurrent with radiotherapy and its mechanisms requires fundamental research to provide experimental evidence for clinical practice. The timing of administration of TKI with radiotherapy includes initiation and cessation times.[39,40] Oral administration of TKI may be initiated before radiotherapy or concomitantly. Administration before radiotherapy considers synchronization of the cell cycle and the steady-state plasma TKI concentration. Concomitant administration with radiotherapy is primarily based on clinical convenience. Initiation of radiotherapy after the drug reaches steady-state plasma concentrations might worsen the clinical condition of a critically ill patient. The duration of oral TKI therapy is also an issue. Some clinical studies have reported that oral TKI therapy was not discontinued after the end of radiotherapy regardless of EGFR mutation status as long as the patient was tolerant until systemic progression was observed, which is worthy of further discussion. For example, the benefits and risks of continuation of oral TKI therapy until systemic progression in patients with wild-type EGFR who have lesions in complete remission after radiation are not known. Administration of an oral TKI concurrent with radiotherapy for one month after radiotherapy is important if radiation sensitization and death in the proliferation phase are considered. The treatment strategy should be individualized one month after the end of radiotherapy in accordance with the patient's clinical situation.[41] The current results of the Phase I clinical dose from the climbing trial are primarily applied to determine the target dose when combined with radiotherapy. However, we need to consider the patient's ability to tolerate the dose and whether the targeted therapy in combination with radiotherapy requires the same concentration as targeted therapy alone. In summary, optimization of targeted therapy with radiotherapy requires further study.

Side effects of molecular targeted therapy with radiation

Most people thought it had better effect and fewer side effects when combining molecular targeted therapy with radiotherapy. However, with increased clinical use of molecular targeted therapy with radiation, people understand the treatment more comprehensively. We also found that it had some side effects which cannot be ignored. For example, when antiangiogenesis drugs are combined with thoracic radiation therapy, serious tracheoesophageal fistula, radiation esophagitis, and radiation pneumonitis may appear.[24,25] Some studies showed that when integration of TKI with molecular targeted therapy applied to clinical, there was a high probability of radioactive pneumonia.[16,21] Did these side effects happen due to the problem of experimental design or targeted

therapy combined with thoracic radiotherapy did increase treatment toxicity? Why did different studies show different types of toxicity? Further exploration are needed which need to cause our attention.

Future prospects

Targeted therapy represents the most important progress made in medical oncology in the 21st century,[42–44] which has also been the fastest-growing period for radiationtherapy. The integrated development of radiotherapy and targeted therapy conforms to the general trends in disciplinary development. Considerable progress has been made with the joint efforts of the two disciplines. Many problems require further investigation, including drug selection, identification of patients likely to derive benefit, timing of drug administration, and the side effects of treatment. However, further fundamental research, accumulation of clinical data, and summaries of the clinical evidence for targeted therapy in combination with radiotherapy will provide a more comprehensive, accurate, and deeper understanding of these therapies. Targeted therapy in combination with radiotherapy has a bright future with broader and more targeted clinical applications.

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Disclosure

The authors report no conflicts of interest in this work.

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